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The rapid progress in host-guest chemistry involving macrocycles has been due in no small part to the availability of reliable and extensive thermodynamic data for a large number of host-guest systems. Although valuable information concerning these systems can be derived from ΔH and ΔS values, few calorimetric data have been reported for host-guest systems. This report summarizes the log K, ΔH, ΔS, and $\Delta \log K$ values for the interaction of a number of chiral 18-crown-6 host molecules for the enantiomers of α-(1-naphthyl)ethylammonium and α-(phenyl)ethylammonium perchlorate salts.

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Quantitation of Enantiomeric Recognition in Chiral Crown Ether-Ammonium Salt Systems

by

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QUANTITATION OF ENANTIOMERIC RECOGNITION IN CHIRAL CROWN ETHER-AMMONIUM SALT SYSTEMS

Macrocycles offer unusual opportunities for the study of molecular recognition. Chiral macrocyclic ligands have also proven to be promising in enantiomeric recognition (refs. 1,2). We have designed and synthesized a series of chiral macrocyclic ligands (refs. 3-5). Some of these ligands have been found to exhibit excellent enantiomeric recognition toward chiral primary ammonium salts (refs. 3-5). Systematic studies on these chiral ligands have been conducted in our laboratory in the hope of understanding the origin of enantiomeric recognition.

Understanding enantiomeric recognition requires that the interactions involved be quantitated. This quantification provides the basis for evaluating guest selectivity and binding strength. Correlation of the quantified properties of host-guest complexes with their molecular structures should provide the basis for understanding host-guest recognition as well as for predicting the ligands which should be synthesized in order to obtain desired selectivities. Others have used various quantities to quantify enantiomeric recognition. One of these quantities is the chromatographic separation factor α which is determined when a macrocycle-containing column is used in the separation of two enantiomers (ref. 6). Other quantities include differences in membrane transport (ref. 7), in extractability (ref. 8), in activation energy of complex dissociation ($\Delta G^{\ddagger}$) (refs. 4,9), and in complex stability (log K) (ref. 3-5). Among these quantities, however, only the complex stability (log K) can be used directly to describe the ability of the chiral ligand to recognize guest enantiomers. Other quantities (except $\Delta G^{\ddagger}$) describe more than one interaction or process, and they are sometimes called 'apparent' quantities. Unless the correlations between these 'apparent' quantities and those for their constituent interactions have been well established, conclusions concerning the causes of chiral recognition cannot be made from such data. Therefore, we have chosen the difference in complex stabilities (Δlog K) as the unique measure for the enantiomeric recognition displayed in our systems. Since Δlog K directly expresses the ability of a chiral ligand to exhibit

enantiomeric recognition, comparison of $\Delta\log K$ values and correlation of $\Delta\log K$ values with the structural and conditional parameters of the chiral systems are considered valid.

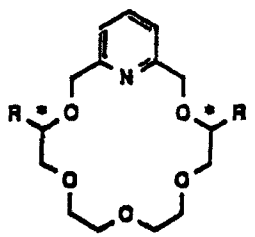
Figure 1 shows some of the chiral macrocyclic ligands we have studied and Table 1 lists the log K and Δ log K values for the interaction of these chiral ligands with enantiomers of some chiral primary ammonium salts. It is seen from Table 1 that chiral ligand **1** shows reasonably good enantiomeric recognition toward chiral naphthyl- and phenylethylammonium cations. Ligands **2** and **3** differ from **1** in that the two methyl substituents in **1** are replaced by two phenyl groups in **2** and two tert-butyl groups in **3**, respectively. Although the size increase from methyl to phenyl does not bring improvement in enantiomeric recognition, the size increase from methyl to tert-butyl improves the extent of enantiomeric recognition significantly. However, the complex stabilities drop sharply as a result of the substitution of methyl groups by tert-butyl groups. Although the $\Delta\log K$ value for **1**-NapEt system is not directly comparable to that for the **3**-NapEt system because the solvents are different, the $\Delta\log K$ increase from 0.24 to 0.71 can still be partly attributed to the effect of substituent size increase because the effect of solvent on enantiomeric recognition is not significant enough to cause this much $\Delta\log K$ increase (ref. 10).

Ligand **4** differs from **1** by having two keto oxygens next to the pyridine ring. Compared to **1**, ligand **4** displayed improved enantiomeric recognition toward NapEt and PhEt. This improvement may be attributed to the increased rigidity of ligand **4**. Replacing the methyl substituents in **4** by phenyl groups leads to significant improvement in enantiomeric recognition by **5** and a slight drop in complex stabilities. Ligand **6** is expected to show even greater improvement in recognition. However, the complex stabilities drop so much that no interaction can be detected.

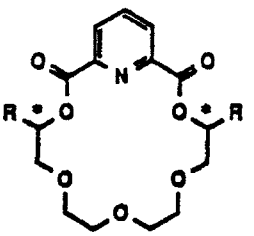
Ligand **7** differs from **1** in that the two chiral centers are located on the same side of the pyridine ring. As expected, ligand **7** displays no enantiomeric recognition toward NapEt. this is probably because the bulky group of NapEt can avoid stearic repulsion by locating on the other side of the pyridine ring where no methyl substituents are present. Ligand **8** differs from **5** by having two chiral centers one

position farther away from the pyridine ring. The recognition displayed by **8** is found to be much smaller than that by **5**. It is evident that the position of chiral centers in the ligand molecule plays a key role in causing enantiomeric recognition.

Fig. 1 Chiral macrocyclic ligands studied



R=Me (1), Ph (2), tBu (3)



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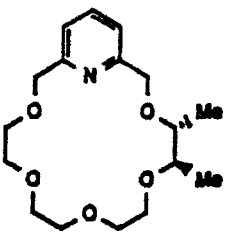

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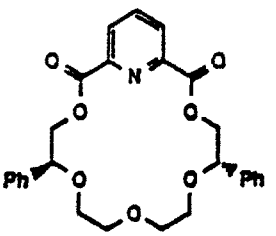

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Table 1. Log K, ΔH, and ΔS values[a] for the interactions of the macrocyclic ligands with enantiomers of several primary ammonium cations at 25° C

Ligand	Cation[b]	Solvt.[c]	Meth.[d]	Log K	ΔH[e]	ΔS[e]	Δ Log K[f]
(SS)-1	(R)-NapEt	M	Cal.	3.00(2)	-29.1(1)	-40.3	
	(S)-NapEt	M	Cal.	2.76(2)	-22.3(1)	-21.8	0.24(4)
	(R)-PhEt	1M/1C	NMR	3.62(5)			
	(S)-PhEt	1M/1C	NMR	3.29(5)			0.33(10)
	(R)-PhEtOH	1M/1C	NMR	3.21(5)			
	(S)-PhEtOH	1M/1C	NMR	3.27(5)			-0.06(10)
(RR)-2	(R)-NapEt	M	NMR	2.92(5)			
	(S)-NapEt	M	NMR	3.10(5)			0.18(10)
	(R)-PhEt	M	NMR	2.91(5)			
	(S)-PhEt	M	NMR	3.10(5)			0.19(10)
(SS)-3	(R)-NapEt	1M/9C	NMR	1.33(5)			
	(S)-NapEt	1M/9C	NMR	0.62(8)			0.71(13)
(SS)-4	(R)-NapEt	M	Cal.	2.47(2)	-27.6(1)	-10.8	
	(S)-NapEt	M	Cal.	2.06(2)	-26.4(1)	-11.3	0.41(4)
	(R)-PhEt	M	NMR	2.33(5)			
	(S)-PhEt	M	NMR	1.88(5)			0.45(10)
(SS)-5	(R)-NapEt	7M/3C	NMR	2.15(6)			
	(S)-NapEt	7M/3C	NMR	<1.30			>0.85
	(S)-PhEt	1M/1C	NMR	2.62(5)			
	(R)-PhEt	1M/1C	NMR	2.06(5)			0.56(10)
	(R)-PhEtOH	1M/1C	NMR	2.24(5)			
	(S)-PhEtOH	1M/1C	NMR	2.95(6)			-0.71(11)
(SS)-6	(R)-NapEt	1M/9C	NMR	N/R			
	(S)-NapEt	1M/9C	NMR	N/R			
(RR)-7	(R)-NapEt	M	NMR	3.00(3)			
	(S)-NapEt	M	NMR	2.94(4)			-0.06(9)
(SS)-8	(R)-NapEt	1M/1C	Cal.	2.57(3)	-29.7(2)	-50.6	
	(S)-NapEt	1M/1C	Cal.	2.35(3)	-44.4(2)	-103	0.22(6)
	(R)-PhEt	M	Cal.	2.58(3)	-17.3(2)	-8.6	
	(S)-PhEt	M	Cal.	2.44(3)	-17.7(2)	-12.8	0.14(6)

[a]Uncertainties are indicated in the parentheses following each value. N/R indicates that the values can not be determined due to lack of significant heat or chemical shift change. [b]Perchlorate salts were used for all of the ammonium cations listed in this table. The notations for the ammonium cations are defined in Figure 3. [c]M = methanol, C = chloroform, 1M/1C = 50% chloroform (v/v). For NMR experiment, 100% deutcrated solvents were used. For calorimetry, non-deuterated solvents were used. [d]NMR = ^{1}H NMR method, Cal. = titration calorimetry. [e]ΔH and ΔS values are in the unites of kj/mol and j/mol/K, respectively. [f]Δlog K = log$K$(*SS-R*) - log$K$(*SS-S*) or log$K$(*RR-S*) - log$K$(*RR-R*).

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